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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/542,121	Applicant(s) RUCH, FRANK	
	Examiner Manjunath N. Rao, Ph.D.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-13 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Claims 1, 3-13, 25-30 are now currently pending and are present for examination in this application.

Applicants' arguments filed on 8-1-02, paper No. 10, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3-5, 10-13, 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Somkuti(a) et al. (Enzyme Microb. Technol., 1994, Vol. 16:573-576), Somkuti(b) et al. (Curr. Microbiol., 1998, Vol. 36:202-206), Herman et al. (In Streptococcal Genetics, Ferrretti and Curtiss(Eds), pages 225-228, 1987), VanBelkum et al. (J. Bacteriol., 1991, Vol. 173(24):7934-7941), Lee et al. (Biotechnol. Bioeng., 1996, Vol. 52(5):572-578) and Chang et al. (US 5,766,907, 6-16-98). See previous Office action for rejection.

In response to the previous Office action, applicants have traversed the above rejection. Applicants argue at length and conclude that the above references do not render claims 1 and 3-5, 10-13, 25-30 obvious. Applicants also argue that Examiner has resorted to hindsight reconstruction. Examiner respectfully disagrees. Applicants argue as if each and every one of

the reference must have disclosed or taught the invention in order to render the invention obvious. However, that is not a requirement for an obviousness rejection. Examiner has indeed used a number of references in order to address specific parts of the invention that were well known in the art. Somkuti (a), (b) et al. and Van Belkum et al. references were used to show that the technique of permeabilization of lactic acid bacteria such that the BG enzyme in the cells would be easily accessible for the hydrolysis of the lactose in the milk product was very well known in the art to solve the problem of lactose intolerance due to consumption of dairy products. However, applicants argue that none of the above references teach recombinant gene under the control of promoter and a BG activity of 4,000 MU, which is not expected of a reference used in an obviousness rejection. Similarly, Herman and Lee et al. references were used to show that the BG gene of *S.thermophilus* was already well known and available as a cDNA for any one skilled in the art for further use or manipulation of the gene. With regard to these references applicants again argue that the references did not make lactic acid bacterium containing the BG gene under the control of a promoter or the references do not disclose BG production of at least 4,0000 MU. Irrespective of what Herman et al. contemplated in their research paper, the cDNA clone of the *S.thermophilus* BG gene was available for any one skilled in the art to be used for any purpose. Similarly Lee et al. reference was used to highlight the fact that it was possible for one skilled in the art to achieve high levels of BG expression, and much more than what applicants have achieved. However, applicants argue that Lee et al. reference teaches production of high levels of BG in *E.coli* transformed with a plasmid comprising a BG gene under the control of "nar" promoter and that that it does not describe the use of lactic acid bacterium or the permeabilization of the cells and that there's no evidence that

the "nar" promoter would work in a lactic acid bacteria. They continue to argue the bacteriological aspects that *E.coli* is Gram negative and that lactic acid bacteria are Gram positive and there is no reason to believe that one skilled in the art would have been motivated to use a "nar" promoter for expression of BG in a lactic acid bacterium. Examiner respectfully disagrees with applicants' argument. Applicants argue as if claim 1 was limited to promoters that work only in lactic acid bacteria. However, a perusal of claim 1 indicates that it is directed to use of any promoter. Furthermore, without evidence or a reference applicant cannot conclude that the promoter of Gram negative bacteria will not work in Gram positive bacteria and that one of skill in the art would not be motivated to do so. There are many promoters which have been successfully used in a wide variety of prokaryotes as well as eukaryotic and mammalian cells. Furthermore, if one found that the "nar" promoter did not function in lactic acid bacteria it clearly would have been obvious to replace the "nar" promoter with a known lactic acid bacterial promoter such as nisA as was discussed in the rejection of claims 6-9. Examiner would like to point out at this stage that applicant has misquoted the Examiner (see the paragraph quoted from the Office action in page 6, para 4-5 in applicant's response) by reciting the rejection paragraphs meant for rejection of claim 6-9 while arguing against the rejection of the above claims. Such misquotation makes the argument only more confusing and misplaced.

Chang et al. reference was used to show the advances in packaging or immobilization of microbial cells which is claimed in claim 29. Even though it was explained in the rejection, it appears that the applicant has missed.

Applicant further argues that the *S.thermophilus* BG is not the most favored in the industry and based on Somkuti et al. reference the industry generally uses the yeast BG.

Examiner made the conclusion that the *S.thermophilus* is the most favored in the industry based on his general survey of the literature and also based on the reference of Lee et al. who have used it for high level production of BG. If the yeasts were the most favored by the industry, as applicants argue, Examiner wonders as to why the yeast gene was not chosen for high level production of BG by Lee et al. Furthermore, even if the yeast gene was being used more frequently in the past, clearly Lee et al. suggest use of *S.thermophilus* gene and that very high levels of BG can be produced therefrom. As such one would have been motivated to select this BG gene for recombinant production. Arguing that *S.thermophilus* BG is not most favored by the industry is not persuasive to overcome the above rejection.

Finally applicant simply recants from the Office action and argues that the rejection is simply a string of connection of components with no explanation of any motivation for such combinations. Examiner respectfully disagrees. Examiner has compiled all the references and provided motivation as to why it would be obvious to one skilled in the art to combine the above references. Some of the motivational statements recanted from the previous Office action are as follows, i.e., one of ordinary skill in the would have been motivated to use ethanol for permeabilization to overcome the residual effects of detergents. Similarly, one would have been motivated to use a lactococcin producing strain of *L.lactis* since lactococcin A is known to increase permeability of the cells which would be an added advantage to permeabilization by ethanol. Similarly one of ordinary skill in the art would be motivated to package the highly permeable, and high BG producing *L.lactis* in immobilized form using calcium alginate method so that the recombinant bacteria can be transported and stored to be used where and when required and also since there is a demand for agents which can be ingested safely and at the same

time hydrolyze lactose in milk and milk products by lactose intolerant people and also due to the fact that the *S.thermophilus* enzyme, with its relatively high (50-55 °C) optimum temperature could replace less-heat-tolerant BG preparations derived from yeasts that are currently used on a commercial scale.

Applicant continues to argue at length as if claims are restricted to a specific promoter that will work in Lactic acid bacteria and improperly recites paragraphs from another rejection. However, as pointed out earlier, claims are **not** to such a promoter and therefore, the reference of Lee et al. which demonstrates the very high level of expression of BG gene is valid reference for rendering the above claim obvious. Therefore, for all the above reasons, the above rejection is maintained.

Applicants finally argue "unexpected results" with respect to hydrolysis of lactose observed at low temperatures. Applicants argue that the permeabilized lactic acid bacteria according to the invention hydrolyzed lactose in milk in less than 6 hours at 4 °C. While this may be so, applicant's use of unexpected results is not commensurate with the scope of the claims. This is because, it appears that the unexpected result is limited to whatever kind of promoter that was used in construction of BG gene and also more importantly to the specific type of lactic acid bacterial species used. It is possible that specific factors in those specific lactic acid bacterial cells enhance the activity of the thermophilic BG (the BG gene from the thermophilic *S.thermophilus*) at low temperatures at which the enzyme is not normally active. Furthermore, applicant has not shown that the high level of BG production can be achieved using **any promoter** in **any lactic acid bacteria** or all the species of the lactic acid bacteria claimed in claim 3. In fact applicant has argued that promoters from Gram negative bacteria

may not work in Gram positive bacteria and as if the promoter used by the applicant is the essence of the invention. Secondly applicant has also not shown that the unexpected results occurred in any or all the lactic acid bacteria including those claimed in claim 3. Until such time, applicant demonstrates support for the above in the disclosure, the use of unexpected results is not persuasive to overcome the above rejection.

Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Somkuti(a) et al. (Enzyme Microb. Technol., 1994, Vol. 16:573-576), Somkuti(b) et al. (Curr. Microbiol., 1998, Vol. 36:202-206), Herman et al. (In Streptococcal Genetics, Ferrretti and Curtiss(Eds), pages 225-228, 1987), VanBelkum et al. (J. Bacteriol., 1991, Vol. 173(24):7934-7941) and Lee et al. (Biotechnol. Bioeng., 1996, Vol. 52(5):572-578) as applied to claims 1 and 3-5, 10-13, 25-30 above, and further in view of Kuipers et al. (US 5,914,248, 6-22-99). See previous Office action for rejection.

In response to the previous Office action applicant has traversed above rejection arguing that she has provided ample argument that claims 1, 3-5, 10-13 and 25-30 are non-obvious and as claims 6-9 depend from claim 1, rejection of claims 6-9 should be withdrawn. Applicant continues to argue that even if arguments for withdrawal of rejection of claim 1 were not adequate, the addition of Kuipers et al. reference cannot make up the deficiencies of the other references. Examiner respectfully disagrees with the applicant that the rejection should be withdrawn. Here again applicant appears to be arguing that each and every reference used in a obviousness type of rejection must teach each and every limitation of the claims. Applicant argues that while the reference of Kuipers et al. discloses a method of gene expression in lactic

acid bacteria by providing a DNA fragment under the control of nisA promoter and the Office action lists a number of advantages of using the nisA promoter, the reference is not a valid reference because it does not teach the use of recombinant BG gene under the control of nisA promoter.

In spite of providing relevant motivational statements by the Examiner for the use of nisA promoter by anyone skilled in the art, applicant continues to argue that there is no reason to believe that one skilled in the art would use the nisA promoter in place of nar promoter as taught by Lee et al. Applicant argues as if it is widely accepted in the art that promoters are specific to Gram positive and Gram negative bacteria without providing any proof to such conclusion. Applicant argues that as Lee et al. used a Gram negative bacteria and a promoter from a Gram negative bacteria and therefore one of ordinary skill in the art would never turn to Lee et al. reference. Examiner respectfully disagrees with such an argument. The fact that Lee et al. demonstrate a very high level of BG production (36,000 M.U.), one of skilled in the art interested in producing very high levels of BG would definitely turn to Lee et al. reference. Applicant's argument that there is no suggestion in the art to employ a nisA to promote expression of a BG gene in spite of the fact that Kuipers et al. teach the promotion of two heterologous genes is highly misplaced and is again arguing that the reference used for an obviousness rejection should teach all the elements of the claims. If such was the case Examiner would have rejected the claims under 35 U.S.C. 102(a) or (b). Examiner has listed a number of motivational reasons among which the following would be one of the more compelling reason for one skilled in the art of making dairy products for human consumption, i.e., the reference teaches that advantageously, while the induction of the **preferred gene** can be obtained as a

positive regulation, only very small amounts i.e., less than 1 microgram/liter of the inducing factor will be required (see column 6) which does not greatly alter the food/milk composition and the antimicrobial activity of nisin is also another added advantage which kills the growth of any opportunistic contaminant in milk. Therefore contrary to applicant's argument the above claims 6-9 would have been *prima obvious* to one of ordinary skill in the art and hence the rejection is maintained.

Conclusion

None of the claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-

5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1652

Manjunath N. Rao
November 26, 2002